EXHIBIT 11

Perineal Talc Use and Ovarian Cancer

A Systematic Review and Meta-Analysis

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Background: It has been posited that there is an association between perineal talc use and the incidence of ovarian cancer. To date, this has only been explored in observational studies.

Objectives: To perform a meta-analysis to evaluate the association between perineal talc use and risk of ovarian cancer.

Methods: Studies were identified using six electronic databases. Observational studies involving at least 50 cases of ovarian cancer were eligible for inclusion. We analyzed the association between ovarian cancer, including specific types, and any perineal talc use, long-term (>10 years) use, total lifetime applications, and use on diaphragms or sanitary napkins. A subgroup analysis was performed, stratifying by study design and population.

Results: We identified 24 case–control (13,421 cases) and three cohort studies (890 cases, 181,860 person-years). Any perineal talc use was associated with increased risk of ovarian cancer (OR = 1.31; 95% CI = 1.24, 1.39). More than 3600 lifetime applications (OR = 1.42; 95% CI = 1.25, 1.61) were slightly more associated with ovarian cancer than <3600 (OR = 1.32; 95% CI = 1.15, 1.50). An association with ever use of talc was found in case–control studies (OR = 1.35; 95% CI = 1.27, 1.43), but not cohort studies (OR = 1.06; 95% CI = 0.90, 1.25). However, cohort studies found an association between talc use and invasive serous type ovarian cancer (OR = 1.25; 95% CI = 1.01, 1.55). We found an increased risk of serous and endometrioid, but not mucinous or clear cell subtypes.

Conclusions: In general, there is a consistent association between perineal talc use and ovarian cancer. Some variation in the magnitude of the effect was found when considering study design and ovarian cancer subtype.

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Ovarian cancer is the gynecologic cancer associated with the highest mortality in the United States, in 2012 being the fifth highest cause of cancer death in women with 14,404 deaths in that country.[1] The National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) predicts that in the United States, in 2016, there will be 22,280 incidences of newly diagnosed ovarian cancer, and 14,240 deaths caused by ovarian cancer based on age-adjusted data from 2009 to 2013.[2] The 5-year survival statistics for ovarian cancer are poor, largely because patients usually present with advanced disease, which is less amenable to curative therapy.[3] SEER estimates that only 15% of patients present with disease localized to the ovary, which contributes to a 5-year survival of 46.2%.[2] It is imperative to develop public health programs, which either reduce the incidence of ovarian cancer or detect it at an earlier stage, to reduce the burden of this disease.

Routine pelvic examinations, transvaginal ultrasonography, and tumor markers have been trialed as potential screening tools for ovarian cancer, but are limited in their usefulness. The cancer marker cancer antigen 125 (CA-125, also known as mucin 16) has been found to be elevated in 80% of all ovarian carcinomas, but this falls to 50% in women in which the cancer is localized only to the ovary, where it is most amenable to treatment.[4] As CA-125 has a low sensitivity and limited specificity, it is not recommended as a screening test for women without clinical symptoms.[5] Ultrasound has a reasonable sensitivity but poor specificity and positive predictive value, particularly as it is poor at distinguishing between benign and malignant masses.[6] While the search for an effective screening regimen for ovarian cancer continues, the importance of primary prevention becomes paramount.

Talcum powder is made of talc, a hydrated magnesium silicate, and is used to absorb moisture on the body. Some women choose to dust talc on the perineum, or apply it to diaphragms or sanitary napkins, to reduce friction, keep the skin dry, reduce odor, and prevent rashes. The potential association between perineal talc use and ovarian cancer has been discussed for decades. The first investigation of this association was performed by Cramer et al[7] in 1982, when the investigators found a relative risk of 1.92 (95% CI = 1.27, 2.89) for ovarian cancer when women either dusted the perineum with talc powder or used it on sanitary napkins. Since this time, there has been substantial interest in and research into this association.

In the present context, the association between talc use and ovarian cancer takes on considerable relevance, as the pharmaceutical and consumer products company Johnson & Johnson has recently had damages levied to the total of US$717 million against them in five law suits. In these cases, juries decided that the use of talcum powder caused or contributed to the development of the plaintiff's ovarian cancer. The evidence for the association between perineal talc use and ovarian cancer is based on the body of knowledge from observational studies, and most of these have been retrospective case–control studies prone to recall bias. Hence, while perineal talc use has not been shown to be safe, in a similar regard, a certain causal link between talc use and ovarian cancer has not yet been established.[8,9]

In 2013, a pooled analysis was performed for eight population-based case–control studies, and found a modest increased risk (OR = 1.24) of ovarian carcinoma associated with perineal talc use.[10] In 2007, a meta-analysis was performed of nine observational studies; however, this study only examined the use of talc on contraceptive diaphragms.[11] The overall finding of this meta-analysis was that the use of talc on contraceptive diaphragms was not associated with ovarian cancer. Meta-analyses have been performed on this subject before; however, the most recent was in 2008,[9] and since this time, the results of a number of large case–control studies and two cohort studies[12,13] have been published. Hence, there is a need to update the literature, particularly considering pending litigation against Johnson & Johnson by other claimants, and Johnson & Johnson's potential plans to appeal the previous decisions. Furthermore, producers of talcum powder products continue to sell these products without any warning labels regarding perineal use and potential associations with ovarian cancer. Hence, there is a need for clarification, to allow women to be adequately informed of the risk of use of these products, possibly preventing future harm.

This paper aims to review the literature and provide an overall risk estimate for the association between perineal talc use and ovarian carcinoma. We will also perform subgroup analyses by the method of talc application, the duration of talc use, the total number of perineal talc applications, and the type of ovarian cancer developed to further elucidate the relationship between talc use and ovarian carcinoma.

METHODS

Study Protocol

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[14] R.P. performed a systematic search of the databases MEDLINE (from 1950), PubMed (from 1946), Embase (from 1949), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), LILACS, and the Cochrane Central Register of Controlled Trials through 22 August 2017 to identify relevant articles. The search used the terms ("talc" OR "talcum powder") AND ("ovarian cancer" OR "ovarian carcinoma"), which were searched as text word and as exploded medical subject headings where possible. We also searched the reference lists of relevant articles for appropriate studies. No language restrictions were used in either the search or study selection. We did not search for unpublished literature.

Study Selection

We included studies that met the following inclusion criteria: (1) the study investigated the perineal use of talc in relation to risk of development of ovarian cancer; (2) the study reported adverse events as an odds ratio (OR), or the data were presented such that an OR could be calculated; (3) the 95% confidence interval (CI) was reported, or the data were presented such that the CI could be calculated; and (4) the study involved a minimum of 50 cases. We excluded studies that did not meet the inclusion criteria.

Data Extraction

One of us (R.P.) performed data extraction using a standardized data extraction form, collecting information on the publication year, study design, number of cases, number of controls, total sample size, population type, country, mean age, number of adjusted variables, the risk estimates or data used to calculate the risk estimates, CIs or data used to calculate CIs, and the type of ovarian cancer. R.P. assessed the quality of the studies using the Newcastle-Ottawa Scale (NOS); however, no studies were excluded on the basis of NOS score.[15] Authors were not contacted for missing data. Adjusted ratios were extracted in preference to nonadjusted ratios; however, where ratios were not provided, R.P. calculated unadjusted ORs and CIs.

Statistical Analysis

One of us (G.D.E.) calculated pooled ORs and 95% CIs for the effect of any perineal talc use with all ovarian cancers using a random effects model.[16] Analyses were also performed based on the method of administration (diaphragm, sanitary napkins), duration of use, and type of ovarian cancer developed (all mucinous, mucinous invasive, mucinous borderline, all serous, serous invasive, serous borderline, endometrioid, clear cell). For long-term talc use, we extracted the odds ratio for the group with the longest duration of talc exposure compared with controls, provided that group used talc for a minimum duration of 10 years. For overall lifetime talc applications, groups within each study were divided into either <3600 lifetime applications, equivalent to less than approximately 10 years of daily use, or >3600 applications. Where a group from a study did not completely fit into this dichotomy, we placed it into the category it most closely fit. Details on the categorization of individual groups are available in eTable 1 (http://links.lww.com/EDE/B261). Odds ratios were pooled for invasive serous, invasive mucinous, borderline serous, and borderline mucinous tumors individually. However, as many studies reported only all mucinous or all serous in a single

group, we also ran analyses for risk associated with all mucinous and all serous tumors. Where a study reported separately as borderline and serous, both odds ratios were included separately in the meta-analysis, to ensure all available data were considered.

We tested heterogeneity with Cochran's Q statistic, with $P < 0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25%, 50%, and 75% corresponded to low, moderate, and high degrees of heterogeneity, respectively.[17] We quantified publication bias using the Egger's regression model,[18] with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to statistical nonsignificance at the $P < 0.05$ level. Publication bias is generally regarded as a concern if the fail-safe number is less than 5n + 10, with n being the number of studies included in the meta-analysis.[19] All analyses were performed with Comprehensive Meta-analysis (version 3·0; Biostat, Englewood, NJ; 2014).

RESULTS

Study Characteristics

We performed a broad literature search of electronic databases, identifying 363 citations for review (Figure 1). Initially, 318 studies were discarded, with many being narrative reviews, duplicates, animal studies, opinion pieces, editorials, or otherwise irrelevant. Forty-five citations were selected for full-text review. Of these, three were excluded due to being associated with endometrial rather than ovarian cancer, two were meta-analyses, five were duplications of data from the same study, one involved non-perineal application of talc, and seven were otherwise irrelevant. No studies were excluded for failing to report an odds ratio or for not providing the necessary raw data from which an odds ratio could be provided. Some studies provided only the raw data, i.e., the number of cases and controls with and without perineal talc use. This allowed an unadjusted odds ratio to be calculated, which was then included in the analysis. Overall, 27 studies were selected. Note that Wu et al[33] (2015) include results from Wu et al[36] (2009); however, only Wu et al[36] (2009) reported on non-perineal talc use, total lifetime applications, and long-term talc use. Hence data were extracted from Wu et al[33] (2015) for the "any perineal use" outcome, and from Wu et al[36] (2009) for the three other outcomes previously mentioned. Hence, while 27 studies were included in the analysis, only 26 were included in the any perineal use analysis. Three studies were cohort studies, including 890 cases and 181,860 person-years.[12,13,20] The remaining 26 studies were case–control studies, with a total of 13,421 cases and 19,314 controls. The case–control studies are described in eTable 1 (http://links.lww.com/EDE/B261), while the cohort studies are described in eTable 2 (http://links.lww.com/EDE/B261). In total, studies involving 14,311 cases of ovarian cancer were included in this review.

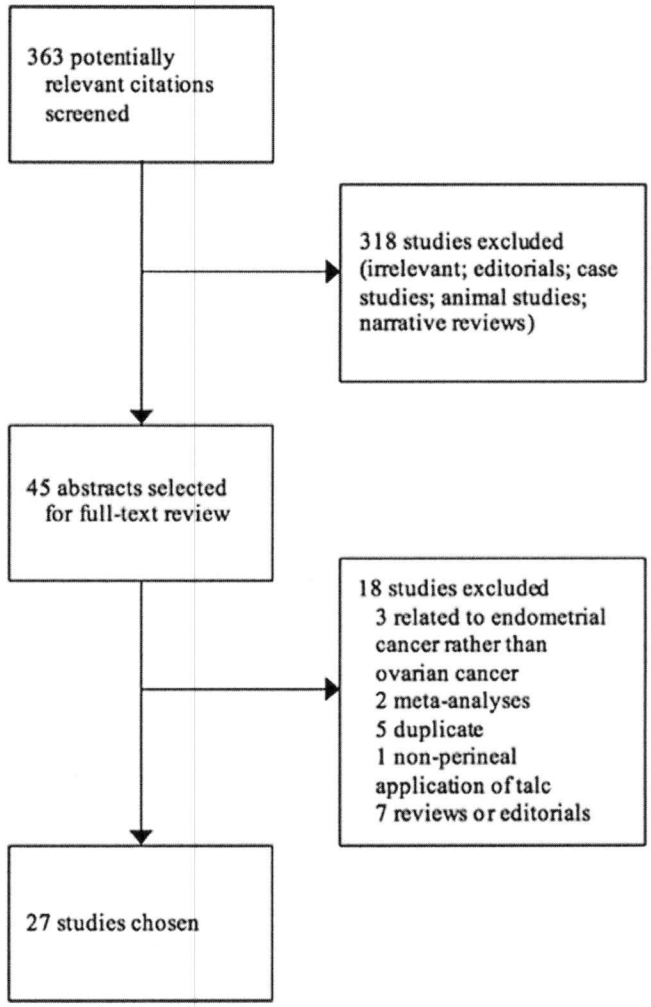

FIGURE 1. PRISMA flowchart for literature search and study selection.

The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS), which involves separate assessment tools for both case–control and cohort studies.[15] The highest score awarded was 8/10, and the lowest was 5/10. The mean score was 7.0. Almost all studies lost points because the exposure to talc was ascertained through self-report rather than an independently verified source, and because the interviewer was not blinded to cases and controls. Many studies also failed to specifically describe that their chosen controls did not have a personal history of previous ovarian cancer. It may be the case that this was done, but not reported in the study methods. Generally, case ascertainment and matching controls based on age and other factors, often geographical location or ethnicity, were well performed in the reviewed studies. The breakdown of individual study scores is included in Tables 1 and 2. Overall, the quality of studies included in

TABLE 1. Summary of Pooled Effect Sizes for Examined Outcome Variables

	No. Studies	Effect Size	Heterogeneity		Publication Bias
		OR (95% CI)	I^2	*P*	*P*
Method of talc use					
Any perineal	26	1.31 (1.24, 1.39)	10.52	0.31	0.09
Any non-perineal	5	1.24 (1.01, 1.51)	66.84	0.02	0.86
Diaphragm	8	0.84 (0.68, 1.05)	14.76	0.31	0.64
Sanitary napkins	12	1.15 (0.94, 1.41)	43.82	0.05	0.17
Length of talc use					
Long-term use (>10 years)	12	1.25 (1.10, 1.43)	45.11	0.04	0.31
<3600 total applications	5	1.32 (1.15, 1.50)	1.83	0.41	0.20
>3600 total applications	5	1.42 (1.25, 1.61)	12.59	0.33	0.40
Type of ovarian cancer					
All serous	10	1.32 (1.22, 1.43)	0.00	0.75	0.44
Serous invasive	5	1.32 (1.13, 1.54)	25.10	0.25	0.75
Serous borderline	3	1.39 (1.09, 1.78)	0.00	0.94	0.83
All mucinous	9	1.12 (0.94, 1.33)	5.79	0.39	0.79
Mucinous invasive	2	1.34 (0.48, 3.79)	69.39	0.07	NA[a]
Mucinous borderline	3	1.18 (0.76, 1.81)	34.07	0.22	0.96
Endometrioid	8	1.35 (1.14, 1.60)	0.00	0.61	0.78
Clear cell	3	1.02 (0.75, 1.39)	0.00	0.78	0.22

[a]NA = not applicable; no publication bias ... result available when there are fewer than three studies in the analysis.

this review was reasonably high. No studies were excluded from the review based on NOS score.

All studies reported at least an odds ratio for any perineal use of talc and its association with ovarian cancer. As previously described, Wu et al[36] (2009) was not included in this analysis to prevent duplication of data. Five studies reported on only non-perineal exposure. Additionally, eight studies provided data for use of talc on a diaphragm, and 12 for sanitary napkins. Twelve studies provided an odds ratio for long-term talc use and its association with ovarian cancer; however, the chosen threshold for long term was variable, from more than 10 years to more than 37.4 years. Five studies reported on the total number of talc applications. It was frequently necessary to report different groups from a single study separately to perform the meta-analysis of this outcome, with the groupings being described specifically in eTable 1 (http://links.lww.com/EDE/B261). Ten studies reported odds ratios for all serous ovarian cancers, five reported for serous invasive cancers, and three reported for serous borderline cancers. Similarly, nine reported for all mucinous cancers, two for mucinous invasive, and three for mucinous borderline. Eight studies reported odds ratios for endometrioid ovarian cancer, and three reported for clear cell ovarian cancer.

Quantitative Data Synthesis

The results of the initial pooling of data from all studies are summarized in Table 1. Pooling of data revealed an increased risk of ovarian cancer associated with any perineal use of talc (Figure 2A; OR = 1.31; 95% CI = 1.24, 1.39). Use of talc long term (>10 years) was also associated with an increased ovarian cancer risk (Figure 2B; OR = 1.25; 95% CI = 1.10, 1.43). Both <3600 total lifetime applications (OR = 1.32; 95% CI = 1.15, 1.50) and >3600 lifetime applications (OR = 1.42; 95% CI = 1.25, 1.61) of talc were associated with an increased risk of ovarian cancer, with a slightly higher risk in the group with greater usage. Talc use on diaphragms or on sanitary napkins was not individually associated with increased risk of ovarian cancer. Any perineal talc use was associated with any serous (Figure 2C; OR = 1.32; 95% CI = 1.22, 1.43), serous invasive (OR = 1.32; 95% CI = 1.13, 1.54), serous borderline (OR = 1.39; 95% CI = 1.09, 1.78), and endometrioid (Figure 2D; OR = 1.35; 95% CI = 1.14, 1.60) subtypes of ovarian cancer, but not the other subtypes.

We performed a subgroup analysis stratifying by study design. It is important to note that there were only three cohort studies, each of which did not report on all the assessed associations. For any perineal talc use, only case–control studies showed an association with ovarian cancer (Figure 2A; OR = 1.35; 95% CI = 1.27, 1.43), while no association was noted for cohort studies (OR = 1.06; 95% CI = 0.90, 1.25). For the other associations assessed, the results are reported in Table 2. In cohort studies, the only association found was between perineal talc use and the incidence of serous invasive cancer subtypes (OR = 1.25; 95% CI = 1.01, 1.55). For borderline serous, borderline mucinous, invasive mucinous, and clear cell ovarian cancer subtypes, no cohort studies provided data for the association and hence the odds ratios reported in eTable 2 (http://links.lww.com/EDE/B261) are derived entirely from case–control studies. The only outcome reported in all three cohort studies was any perineal talc use; hence the available data from prospective studies were limited.

A subgroup analysis related to study population setting, i.e., in the hospital or in the general population, was performed for any perineal talc application. Generally, hospital-based studies were older (pre-2000) than the community-based studies. There were seven hospital-based studies, all of which were case–control studies. There were 20 population-based studies, including 17 case–control studies and all three cohort studies. There was no difference between the pooled results for hospital- and population-based studies (OR = 1.22 vs. 1.33), respectively.

There was heterogeneity in the analysis of non-perineal applications of talc (I^2 = 66.84; P = 0.02). There was no heterogeneity for any of the other outcome measures in either the meta-analysis of all available studies or the subgroup analyses. There was no publication bias in the meta-analysis of any genital talc exposure and ovarian cancer, which included all the studies in the review, except Wu et al[36] (2009) (Figure 3; P = 0.09). The result for publication bias for each of the individual analyses is included in Table 1.

TABLE 2. Summary of Pooled Effect Sizes in Subgroup Analysis by Study Design

	Case–Control Studies (n = 24)				Cohort Studies (n = 3)			
		Effect Size	Heterogeneity			Effect Size	Heterogeneity	
	No. Studies	OR (95% CI)	I^2	*P*	No. Studies	OR (95% CI)	I^2	*P*
Method of talc use								
Any perineal use	23	1.35 (1.27, 1.43)	0.00	0.77	3	1.06 (0.90, 1.25)	18.89	0.29
Non-perineal use	5	1.24 (1.01, 1.51)	66.84	0.02	0	NA	NA	NA
Diaphragm	7	0.81 (0.61, 1.08)	21.92	0.26	1	0.92 (0.68, 1.24)	0.00	1.00
Sanitary napkin	10	1.27 (0.98, 1.65)	40.49	0.09	2	0.93 (0.77, 1.13)	0.00	0.77
Length of talc use								
Long-term use	11	1.29 (1.13, 1.47)	40.53	0.08	1	0.98 (0.75, 1.29)	0.00	1.00
<3600 total applications	5	1.32 (1.15, 1.50)	1.83	0.41	0	NA	NA	NA
>3600 total applications	5	1.42 (1.25, 1.61)	12.59	0.33	0	NA	NA	NA
Type of ovarian cancer								
All serous	12	1.34 (1.23, 1.47)	0.00	0.71	2	1.19 (0.97, 1.47)	0.00	0.61
Serous invasive	3	1.36 (1.05, 1.75)	47.96	0.15	2	1.25 (1.01, 1.55)	0.00	0.33
Serous borderline	3	1.39 (1.09, 1.78)	0.00	0.94	0	NA	NA	NA
All mucinous	9	1.15 (0.93, 1.41)	21.03	0.26	2	0.96 (0.61, 1.53)	0.00	0.84
Mucinous invasive	2	1.34 (0.48, 3.79)	69.39	0.07	0	NA	NA	NA
Mucinous borderline	3	1.18 (0.76, 1.81)	34.07	0.21	0	NA	NA	NA
Endometrioid	6	1.39 (1.16, 1.66)	0.00	0.52	2	1.09 (0.66, 1.80)	0.00	0.48
Clear cell	3	1.02 (0.75, 1.39)	0.00	0.78	0	NA	NA	NA

NA = not applicable; no cohort studies reported on the relevant associations.

DISCUSSION

The present meta-analysis reports a positive association between perineal talc use and ovarian cancer, specifically of the serous and endometrioid histologic subtypes. The mechanism by which perineal talc use may increase the risk of ovarian cancer is uncertain. It has been previously proposed that talc, as a foreign body, may ascend from the vagina through to the uterine tubes and instigate a chronic inflammatory response, which may predispose to the development of ovarian cancer. It is argued that cellular injury, oxidative stress, and local increase in inflammatory mediators such as cytokines and prostaglandins may be mutagenic and hence promote carcinogenesis.[21] In support of this hypothesis, it has been found that hysterectomy or bilateral tubal ligation, in which ovarian exposure to inflammatory mediators would be significantly curtailed, is associated with a reduced risk of ovarian cancer.[22–24] However, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is not inversely associated with the incidence of ovarian cancer, as may be expected if the etiology was related to chronic inflammation.[25,26] It has also been found that human epithelial ovarian cells have an unusually low expression of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), which would reduce their sensitivity to the action of NSAIDs.[27] The potential mechanism by which genital talc is associated with an increased risk of ovarian cancer hence remains unclear.

An important finding of this study is that talc use appears to be associated with increased risk of serous ovarian cancer, of both invasive and borderline types, and not with mucinous ovarian cancer. Additionally, endometrioid ovarian cancers but not clear cell cancers were significantly associated with perineal talc use. Intriguingly, a meta-analysis examining the effects of tubal ligation of ovarian cancer risk found a reduced risk of the same subtypes of ovarian cancer as mentioned here: serous and endometrioid, but not mucinous.[24] If chronic inflammation due to ascending foreign bodies is indeed the mechanism by which talc use is associated with increased ovarian cancer risk, then these results fit the picture. The results for non-perineal application of talc were still positive but of lower magnitude, supporting the hypothesis of ascending foreign bodies causing chronic inflammation. It is plausible that non-perineal application of talc may cause increased risk through, e.g., the respiratory tract. Unfortunately, the evidence remains insufficient to understand the mechanism with any reasonable certainty.

We also found a slightly greater increased risk of ovarian cancer with >3600 lifetime applications compared with those with <3600 lifetime applications. The number of lifetime applications is a more valid measure of the patient's exposure to perineal talc than either duration or frequency of use alone. This finding also supports the chronic inflammatory hypothesis, as repeated exposure would induce a longer period of chronic inflammation, and therefore should increase the predisposition to the development of ovarian cancer. It is notable that these data were only available from

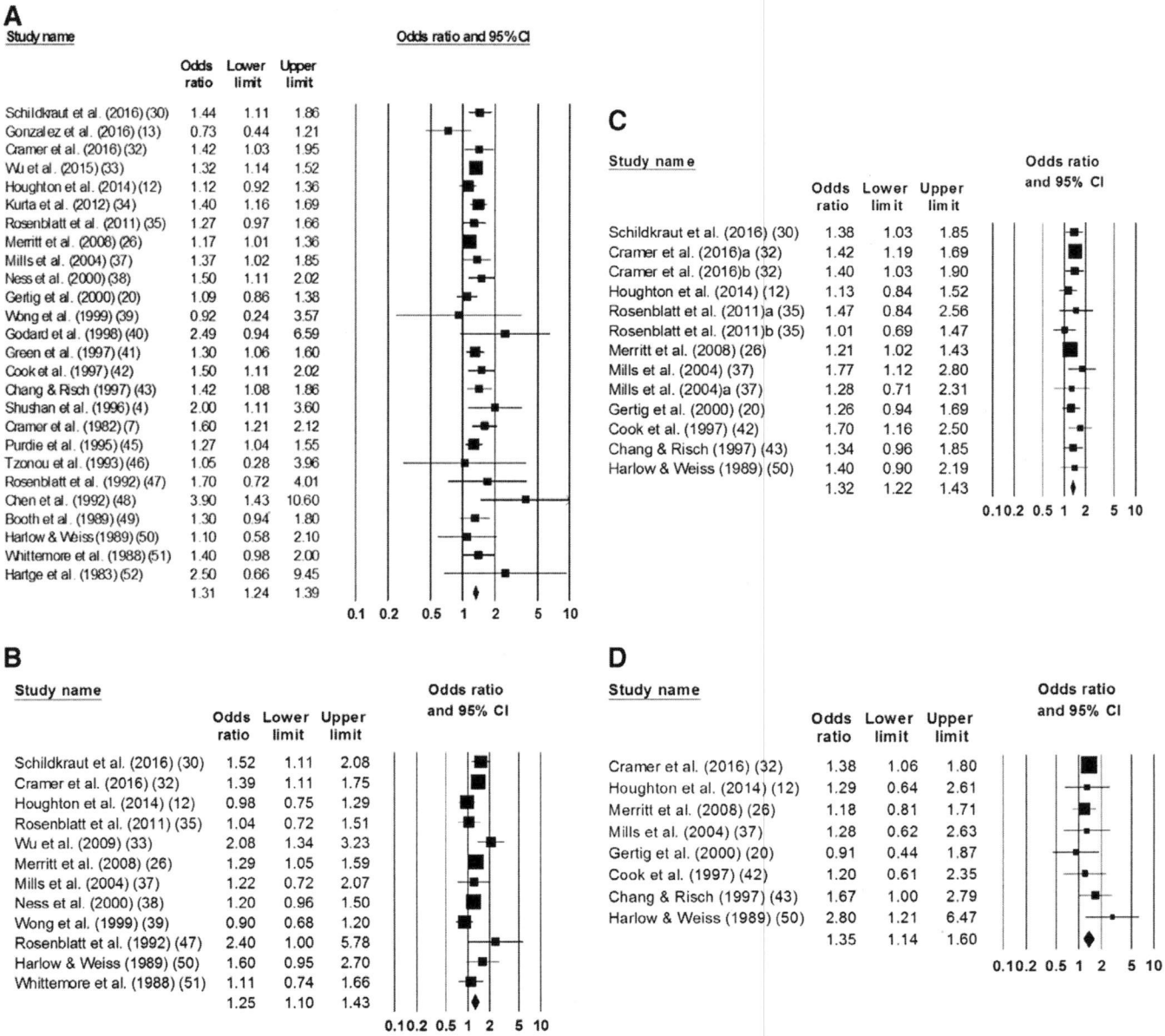

FIGURE 2. A, Any perineal talc use is associated with an increased risk of any ovarian cancer (OR = 1.31; 95% CI = 1.24, 1.39). B, Long-term perineal talc use (>10 years use) is associated with an increased risk of any ovarian cancer, but of a lower magnitude than any perineal use (OR = 1.25; 95% CI = 1.10, 1.43). C, Any perineal talc use is associated with an increased risk of serous ovarian cancers (OR = 1.32; 95% CI = 1.22, 1.43). D, Any perineal talc use is associated with an increased risk of endometrioid type ovarian cancers (OR = 1.35; 95% CI = 1.14, 1.60).

case–control studies, as the three cohort studies did not sufficiently record duration and frequency of use to be included in the analysis. This retrospective finding is therefore prone to recall bias.

This meta-analysis had several strengths. None of the analyses in this review had statistically significant heterogeneity, except for non-perineal application, which indicates consistency in the direction and magnitude of the effect size between individual studies, and strengthening the reliability of the pooled effect sizes. Another strength of this review is the large number of overall cases (n = 14,311), improving the power of the meta-analysis to detect a relatively small effect size, as occurred in this case. Another strength of this review is that the included studies were of relatively high quality as assessed through the NOS, reducing the potential for bias in the conclusions drawn. The NOS revealed that the most common limitations of the included case–control studies were the failure to blind interviewers to case–control status of subjects in the interview, and reliance on memory and self-report for collection of data on perineal talc use.

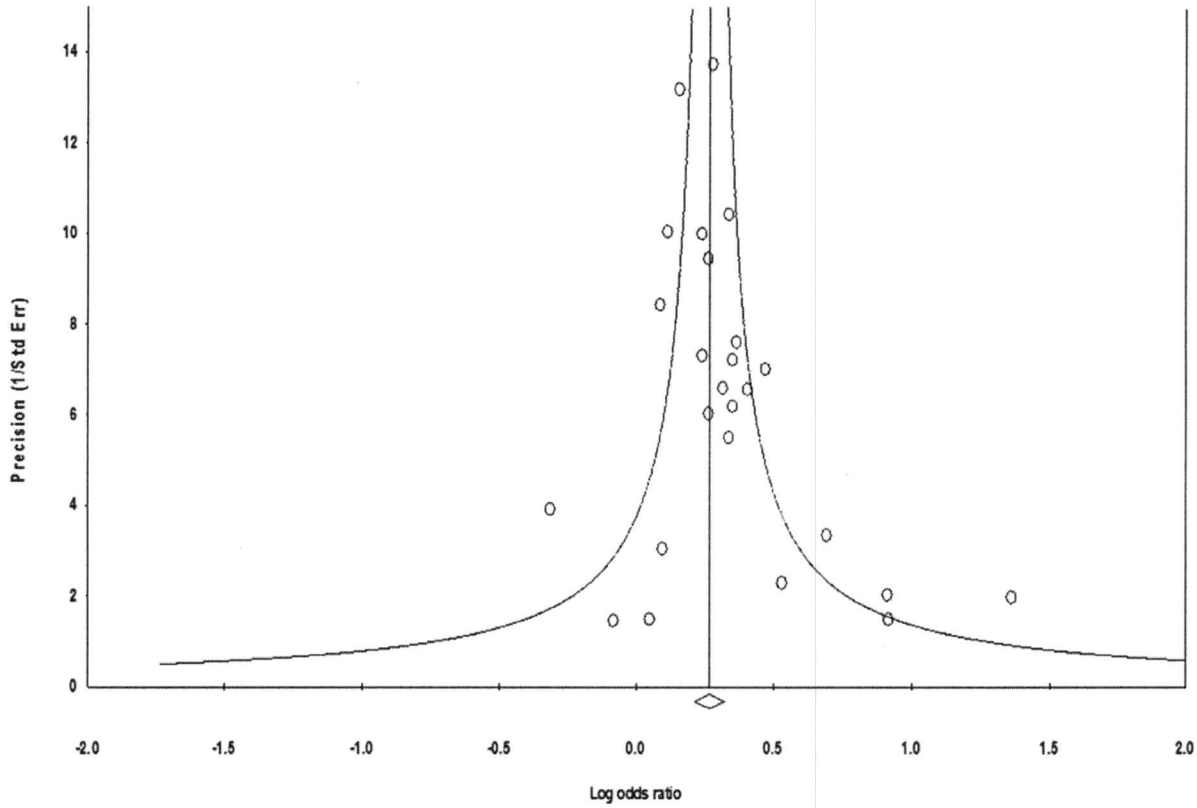

FIGURE 3. Funnel plot for the meta-analysis of studies examining any perineal talc use and risk of ovarian cancer ($P = 0.09$).

A limitation of this study is that it pools nonrandomized studies, primarily case–control studies. The retrospective nature of case–control studies introduces the potential for recall bias. In this case, it is entirely possible that patients with ovarian cancer may be more aware of their previous talc use and hence be more likely to report higher past use. It is possible to attempt to overcome this by blinding the participants to the nature of the study, usually by asking spurious questions; however, the effectiveness of this approach may be limited.[28] Many of the studies in this review recorded data about talc use as part of a more extensive questionnaire focused on other associations, which may reduce the potential for recall bias. However, since the initiation of lawsuits in 2014, there has been extensive media coverage regarding this association, and the potential for recall bias in case–control studies conducted since then may be exacerbated.

Cohort studies are useful in that they are prospective; however, the low incidence of ovarian cancer results in relatively small number of cases even in large cohorts, as seen in the three cohort studies included in this review.[29] Considering potential exposure misclassification issues in case–control studies, the effect for any perineal talc use was very weak in a small number of cohort studies. However, an association between talc use and serous invasive ovarian cancer was found.

Of the studies in this review, case–control studies achieved much large number of cases, in some instances in excess of 2000 cases and a similar number of age-matched controls, which provide greater statistical power for the detection of an effect size of small magnitude. Hence while case–control studies are low-level evidence, they have been preferred in the investigation of the association between talc use and ovarian cancer. They also have the important advantage of not requiring 15 or more years of follow-up, as is necessary for a cohort study to sufficient detect cases of ovarian cancer relative to certain exposures. One potential way to overcome this limitation in future studies is to ensure that talc use is always included in questionnaires of any cohort studies investigating ovarian cancer. It is important not only that talc use be investigated but also the precise location, duration, and frequency of use. As it stands, a meta-analysis of observational studies such as the present study provides the highest level of evidence practically feasible for this research question.

CONCLUSIONS

The results of this review indicate that perineal talc use is associated with a 24%–39% increased risk of ovarian cancer. While the results of case–control studies are prone to recall bias, especially with intense media attention following the commencement of litigation in 2014, the confirmation of an association in cohort studies between perineal talc use and serous invasive ovarian cancer is suggestive of a causal association. Additional epidemiologic evidence from prospective

studies with attention to effects within ovarian cancer subtype is warranted. There is a substantial need for further research on a potential mechanism by which ovarian cancer may be caused by talc, as this will allow a causal relationship to be established or rejected with more certainty. However, particularly because of the dearth of screening tests available for this high-mortality cancer, it is important that research into this association continue as it is a potential avenue for cancer prevention.

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Study	Year	Country	Cases (n)	Controls (n)	Mean Age	Participants	Participant Setting	Relevant Outcomes	NOS[a] score
Schildkraut et al. [30]	2016	U.S.	584	745	NR	African-American women aged 20 to 79 with confirmed invasive epithelial ovarian cancer	Population	Any perineal use; non-perineal use; long-term use (>20yr); <3600/>3600 lifetime applications; all serous	8
Cramer et al. [13]	2016	U.S.	2041	2100	NR	Women aged 18-80 with confirmed epithelial ovarian cancer	Population	Any perineal use; non-perineal use; long-term use (>20yr); <3600/>3600 lifetime applications; serous invasive; serous borderline; mucinous borderline; mucinous invasive; endometrioid; clear cell	7
Wu et al. [33]	2015	U.S.	1701	2391	NR	Women aged 18-74 with confirmed epithelial ovarian cancer	Population	Any perineal use	7
Kurta et al. [34]	2012	U.S.	902	1802	NR	Women at least 25yo with confirmed epithelial ovarian cancer, within 9 months of diagnosis	Population	Any perineal use	8
Rosenblatt et al. [35]	2011	U.S.	812	1313	NR	Women aged 35-74 with diagnosed epithelial ovarian cancer	Population	Any perineal use; sanitary napkin; diaphragm; long-term use (>20yr); <3600/>3600 lifetime applications; mucinous borderline; serous borderline; serous invasive	7
Wu et al. [36]	2009	U.S.	609	688	NR	Women aged 18-74 with	Population	Non-perineal use; long-	8

						histologically confirmed epithelial ovarian cancer		term use; <3600/>3600 lifetime applications;	
Merritt et al. [26]	2008	Australia	1576	1509	57.1	Women aged 18-79 with confirmed cases of epithelial ovarian cancer	Population	Any perineal use; long-term use (>25yr); any serous; any mucinous; endometrioid; clear cell	8
Mills et al. [37]	2004	U.S.	256	1122	55.3	Women with confirmed cases of epithelial ovarian cancer	Population	Any perineal use; long-term use (>30yr); serous invasive; serous borderline; mucinous invasive; mucinous borderline; endometrioid; clear cell	8
Ness et al. [38]	2000	U.S.	767	1367	NR	Women aged 20-69 with epithelial ovarian cancer	Population	Any perineal use; non-perineal use; sanitary napkin; diaphragm; long-term use (>10yr)	8
Wong et al. [39]	1999	U.S.	499	755	54.9	Women with primary epithelial ovarian cancer	Hospital	Any perineal use; long-term use (>20yr); sanitary napkin	5
Godard et al. [40]	1998	Canada	170	170	56.3	Women aged 20-84 with histologically confirmed primary ovarian cancer	Population	Any perineal use	6
Green et al. [41]	1997	Australia	824	855	NR	Women aged 18-79 with primary epithelial ovarian cancer	Population	Any perineal use	8
Cook et al. [42]	1997	U.S.	313	422	NR	White women aged 20-79 with epithelial ovarian cancer	Population	Any perineal use; <3600/>3600 lifetime applications; sanitary napkin; diaphragm	6
Chang & Risch [43]	1997	Canada	450	564	57.5	Women aged 35-79 with histologically confirmed primary ovarian cancer	Population	Any perineal use; sanitary napkin; all serous; all mucinous; endometrioid	6

Shushan et al. [4]	1996	Israel	200	408	NR	Women with confirmed epithelial ovarian cancer	Population	Any perineal use	7
Cramer et al. [31]	1995	U.S.	450	454	NR	Women with histologically confirmed epithelial ovarian cancer	Population	Any perineal use	7
Purdie et al. [45]	1995	Australia	824	860	55.1	Women aged 18-79 with histologically confirmed primary ovarian cancer	Population	Any perineal use	8
Tzonou et al. [46]	1993	Greece	189	200	NR	Women <75 who underwent surgery for epithelial ovarian cancer	Hospital	Any perineal use	5
Rosenblatt et al. [47]	1992	U.S.	77	46	NR	Women with newly diagnosed ovarian cancer	Hospital	Any perineal use; diaphragm; sanitary napkin; long-term use (>37.4yrs)	7
Chen et al. [48]	1992	China	112	224	48.8	Women with newly diagnosed ovarian cancer	Population	Any perineal use	8
Booth et al. [49]	1989	U.K.	235	451	51.7	Women aged <65 with histologically diagnosed epithelial ovarian cancer	Hospital	Any perineal use	6
Harlow & Weiss [50]	1989	U.S.	116	158	NR	White women aged 20-79 with mucinous or serous borderline tumours diagnosed in 1980-1985	Population	Any perineal use; diaphragm; sanitary napkin	7
Whittemore et al. [51]	1988	U.S.	188	539	NR	Women aged 18-74 with primary epithelial ovarian cancer	Hospital	Any perineal use; long-term use (>10yrs); diaphragm	8
Hartge et al. [52]	1983	U.S.	135	171	NR	Epithelial ovarian cancer cases in participating hospitals	Hospital	Any perineal use; non-perineal use; diaphragm	6

NR = not reported

[a] Newcastle-Ottawa Quality Assessment Scale, which rates non-randomized studies based on selection, comparability, and exposure. Maximum score of 10.

eTable 1: Study and study participant characteristics for case-control studies.

Study	Year	Country	Included Participants (n)	Cases (n)	Participant Person-Years	Mean Age at Baseline	Participants	Participant Setting	Relevant Outcomes	NOS[a] score
The Sister Study, as reported in Gonzalez et al. (2016) [13]	2016	U.S. and Puerto Rico	41 654	154	NR	54.8	Women aged 35 to 74 years at enrolment each with a full- or half-sister who had been diagnosed with breast cancer	Population	Any perineal use	6
Women's Health Initiative Observational Study, reported in Houghton et al. (2014) [12]	2014	U.S.	61 576	429	757 291	63.3	Postmenopausal women 50 to 79 at the time of enrolment	Population	Any perineal use; long-term use (>10yr); sanitary napkin; diaphragm; serous invasive; any mucinous; endometrioid	7
Nurses' Health Study, reported in Gertig et al. (2000) [20]	2000	U.S.	78 630	307	984 212	NR	Female registered nurses aged 30-55 at enrolment	Population	Any perineal use; sanitary napkin; any serous; serous invasive; endometrioid; any mucinous	6

NR = not reported

[a] Newcastle-Ottawa Quality Assessment Scale, which rates non-randomized studies based on selection, comparability, and exposure. Maximum score of 10.

eTable 2: Study and study participant characteristics for cohort studies.